SCIENTIFIC LETTER

The mechanism of formation of pulmonary arteriovenous malformations associated with the classic Glenn shunt (superior cavopulmonary anastomosis)

H Ashrafian, L Swan

Heart 2002;**88**:639

Anastomosis of the superior vena cava to the right pulmonary artery (classic Glenn shunt), although initially a successful procedure, is complicated by the development of troublesome diffuse microvascular and potentially lethal macrovascular pulmonary arteriovenous malformations (PAVMS) in up to 25% of cases. The pathogenesis of PAVMS is unclear but has been tentatively attributed to either the absence of pulsatile pulmonary blood flow or the absence of hepatoenteric effluent in the right lung.[1] Evidence favours the latter suggestion. Firstly, other forms of cavopulmonary connection result in loss of pulsatile pulmonary flow but are not associated with a high incidence of PAVMS. Secondly, PAVMS are seen with other congenital cardiac conditions where hepatic blood flow is excluded from the pulmonary circulation and regress when hepatic flow is re-established.[2]

A well recognised association exists between liver disease and PAVM formation (hepatopulmonary syndrome). Hepatic dysfunction in this context has been presumed to alter hepatic blood content and hence predispose to PAVMS. Although no candidate for the defect in the hepatic effluent has been identified, factors that modulate vasodilators, such as prostacyclin, have been proposed. However, no evidence or possible mechanism has been forthcoming.

We suggest that a dynamic balance exists between vasodilators (for example, nitric oxide (NO)) and vasoconstrictors (for example, endothelin 1 (ET-1)) that in addition to regulating vascular tone, chronically remodels vascular architecture. NO, with its protean manifestations of modulating apoptosis, smooth muscle proliferation and angiogenesis, reduces vascular proliferation and predisposes to a more dilated, less resistive pulmonary circulation. This role is supported by transgenic studies of mice overexpressing NO, which demonstrate reduced vasoconstriction in pulmonary hypoxic models.[3] This is a particularly pertinent model as in hepatopulmonary syndrome an excess of pulmonary NO leads to a similar impaired constrictive response to hypoxia and to PAVM formation.

NO is regulated by members of transforming growth factor β (TGF-β) polypeptide superfamily.[4] That this superfamily is critical to PAVM formation is exemplified by hereditary haemorrhagic telangiectasia (HHT), a disease of disordered vascular architecture, an important component of which is PAVMS. Recently the pathogenesis of HHT has been elucidated by the identification of mutations in endoglin and activin receptor-like kinase 1 (ALK-1)—both critical receptors in the TGF-β superfamily.[5]

We contend that members of the TGF-β superfamily, or more precisely their antagonists, are plausible candidates for pulmonary labile humoral factors that exist in functional concentrations in the hepatic effluent. Fractionation of hepatic effluent and bioassay for TGF-β antagonism may identify this elusive "hepatic factor". Although resolving the PAVM issue, another fundamental question is raised: why is the pulmonary circulation somatically modulated by the hepatopulmonary axis?

Authors' affiliations
H Ashrafian, L Swan, Adult Congenital Heart Disease Programme, Royal Brompton Hospital, London, UK

Correspondence to: Houman Ashrafian, c/o Dr L Swan, Adult Congenital Heart Disease Programme, Royal Brompton Hospital, London, SW3 6NP, UK; ashrafian@hotmail.com

Accepted 21 May 2002

REFERENCES

1 **Srivastava D**, Preminger T, Lock JE, *et al*. Hepatic venous blood and the development of pulmonary arteriovenous malformations in congenital heart disease. *Circulation* 1995;**92**:1217–22.
2 **Lee J**, Menkis AH, Rosenberg HC. Reversal of pulmonary arteriovenous malformation after diversion of anomalous hepatic drainage. *Ann Thorac Surg* 1998;**65**:848–9.
3 **Ozaki M**, Kawashima S, Yamashita T, *et al*. Reduced hypoxic pulmonary vascular remodeling by nitric oxide from the endothelium. *Hypertension* 2001;**37**:322–7.
4 **Lopez Farre A**, Mosquera JR, Sanchez de Miguel L, *et al*. Endothelial cells inhibit NO generation by vascular smooth muscle cells. Role of transforming growth factor-beta. *Arterioscler Thromb Vasc Biol* 1996;**16**:1263–8.
5 **Shovlin CL**, Guttmacher AE, Buscarini E, *et al*. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000;**91**:66–7.

Abbreviations: ALK-1, activin receptor-like kinase 1, ET-1, endothelin 1; HHT, hereditary haemorrhagic telangiectasia; NO, nitric oxide; PAVMS, pulmonary arteriovenous malformations; TGF-β, transforming growth factor β